REMARKS

Claims 20-25 and 29-46 were pending and examined. All of the claim were rejected under one of several grounds. Additionally, certain objections to the specification and claim 21 were made.

Applicants have amended claim 20, inserting the subject matter of claims 21 and 22, and, accordingly, are canceling claim 21 and 22.

Claim 25 is amended to define the instructions of the kit differently. The language is supported, for example at pages 4-6 of the specification which discloses the specific genotypes associated with patient outcome and supports instructions for how the kit's user would predict the subject's ability to recover by interpreting the results obtained.

Claim 31 is amended voluntarily for the sake of brevity.

Claim 33-35 are amended to correct their dependency.

Claim 36 is amended to introduce all the polymorphic sites that the kit is designed to test, similar to the amendment to claim 20. Note that this claim is limited to the inclusion of oligonucleotides in the kit.

The dependency of claims 45 and 46 is amended (from claim 29 to claim 36.

None of the amendments introduce new matter and their entry is respectfully requested.

I. OBJECTION TO SPECIFICATION AND CLAIMS

A. The disclosure was objected to because it contains an embedded hyperlink on page 39, line 16. Applicants are asked to inspect the rest of the application and to delete the embedded hyperlink and/or other form of browser-executable code.

Applicants' Response

The specification is amended to delete all occurrences of executable code/hyperlinks

B. Claim 21 was objected to because it was drawn to polymorphic sites in linkage disequilibrium ("**LD**") with position 12580 but then recites 12580 as one of the positions.

Applicants' Response

Applicants are canceling claim 21 and have moved all of the recited polymorphisms, *i.e.* position 12580 and certain positions in LD therewith, into amended claim 20. The objected-to error is no longer present.

II. REJECTIONS UNDER SC § 112, 2nd PARAGRAPH (Indefiniteness)

Claims 33-35 were rejected as indefinite for reciting "the technique" (claims 33-34) and "the determining" (claim 35), both of which lack antecedent basis.

Applicants' Response

Applicants note that these clerical errors have been corrected by amending Claims 33-35 to depend from claim 32. This rejection is therefore moot.

III. REJECTIONS UNDER 35 USC § 112, 1st PARAGRAPH (Written Description)

Claims 20, 22-25 and 29-35 were rejected as failing to comply with the written description requirement.

These claims are drawn to a kit for determining the genotype of a subject at a polymorphic site at nucleotide position 12580 of SEQ 10 NO:1 or a site in LD therewith, which genotype is prognostic of the subjects ability to recover from an inflammatory condition. The Office contends that when these claims are analyzed in light of the specification, they encompasses an "enormous number" of nucleotide molecules. The specification teaches that polymorphic sites 5645, 7121, 7437, 8070, 8406, 9463, 9466, 12219, 13889 and 14440 are in LD with position 12580.

The Office's analysis of "written description" first seeks to determine whether a representative number of species have been described by full structure and asserts that the instant specification teaches 10 nucleic acid sequences. The Action notes that the presence of claim 21 "clearly indicates" that the polymorphisms in LD with position 12580 of SEQ ID NO:1 is broader than those specifically recited since it encompasses any polymorphism that is at any level of LD and thus encompasses every nucleotide in the genome.

The next step of the analysis determines whether a representative number of species have been sufficiently described by other relevant identifying characteristics (*e.g.*, sequence or position within a specific gene or nucleic acid), and whether specific features and functional attributes that would distinguish different members of the claimed genus are disclosed.

Allegedly, the instant specification provides no structural limitations to identify polymorphic sites in LD with position 12580 of SEQ ID NO:1, other than the polymorphisms specifically disclosed at position 5645, 7121,7437,8070,8406,9463, 9466, 12219, 13889 and 14440. The claims read in light of the specification encompass any nucleic acid molecule that can broadly be interpreted as in any level of LD with position 12580 of SEQ ID NO:1. This is said to broadly

encompass "every nucleotide in the genome" as all nucleotides in the genome are in "some level" of LD with every other nucleotide in the genome. In the current situation, the claims allegedly define the "compound" solely based on its functional utility -- polymorphisms in LD with position 12580 of SEQ ID NO:1, without any definition of the particular polymorphisms claimed. One of skill in the art allegedly "cannot envision the detailed chemical structure of the nucleic acids encompassed polymorph isms in LD with position 12580 of SEQ ID NO:1."

The Office concluded that the limited disclosure regarding polymorphisms in LD with position 12580 of SEQ ID NO:1 is not sufficient to reasonably convey to one skilled in the art the scope of the nucleic acid molecules claimed; thus, the specification does not provide adequate written description for the claims.

Applicant's Response

While not agreeing with the Office's position and analysis, Applicants have nevertheless amended claim 20 to be limited to the polymorphisms identified in the application as filed which the Office Action specifically acknowledged (above). Claim 36 has been similarly amended, voluntarily, and now recites specific genotypes (even though it was not rejected under this ground).

In view of these amendments, the §112, first paragraph rejection no longer applies and the rejection may properly be withdrawn.

IV. REJECTION UNDER 35 USC § 102 (ANTICIPATION)

Claims 20, 23, 24, 25, 30, 32, 33 were rejected under 35 U.S.C.§ 102(b) as anticipated by **Henry** *et al.* *(Arterioscler. Thromb. Vasc. Biol.* (1998) *19*:84-91) (hereinafter "**Henry**").

The Action refers to MPEP 2111.02 regarding the position that the preamble is not considered a limitation if the body of the claim fully recites all of the limitations. Accordingly, the language in claim 1 reciting "a kit useful for determining a genotype of a subject ….. at nucleotide position 12580 of SEQ ID NO:1" is considered merely to set forth an intended use/purpose of the claimed kit, without limiting the scope (beyond reciting position 12580 of SEQ ID NO:1.)

Claims 20, 23, 24, 25, 30, 32, 33 allegedly do not contain structural requirements to distinguish them from a composition. The term "kit" is allegedly not defined to be so limited in the specification. Accordingly, the Office interprets the claim reasonably to encompass a composition containing the claimed molecule.

As to the limitation that the kit contains instructions, the inclusion of instructions is not considered to provide a patentable limitation because the instructions merely represent a statement of intended use in the form of instructions in a kit, citing *In re Ngai,* 367 F.3d 1336,70 USPQ2d 1862 (Fed. Cir. 2004) for the proposition that "an inventor could not patent known kits by simply attaching new set of instructions to that product".

(Applicants note that the foregoing quote in the Office Action is not a direct quote from the published decision.)

According to the Action, **Henry** teaches PCR amplification followed by restriction enzyme cleavage to detect polymorphisms in PAI-1 (page 85, 2nd col.). The Office concluded that **Henry** teaches "a kit for detection a polymorphisms in LD with position 12580 of SEQ ID NO:1 by use of primers and a restriction enzyme."

Applicants' Response

Amended claim 20 recites only the specific polymorphisms being claimed and is thus no longer anticipated by **Henry** which teaches detection only of the 4G/5G polymorphism of PAI-1 which was only disease-associated polymorphism known prior to the present invention, but is not one included a in the amended claims. Therefore, the present claims are free of **Henry**, and this ground for rejection may properly be withdrawn.

V. REJECTIONS UNDER 35 USC § 103 (OBVIOUSNESS)

A. First Obviousness Rejection

Claims 20, 30, 34, 36, 37 and 39 were rejected as being obvious over **Menges *et al.*** (*Lancet* (2001) *357* 1096-7) (hereinafter "**Menges**") in view **Xu *et al.*** (WO2001/81631, pub. 01/11/2001, cited in IDS) (hereinafter "**Xu**") and GenBank Accession AF386492.2 GI:14488407 (June 19, 2001) (hereinafter "**GenBank Sequence**"). The Action also refers here to MPEP2111.02, discussed above and discusses the fact that the (present) preamble is not considered to be limiting.

Again, as above, the Action contends that the rejected claims, despite reciting the term "kit", **contain** no structural requirements to distinguish such a kit from a composition. Accordingly, the Office has interpreted the claim as encompassing a composition containing the claimed molecules.

As above, the limitation that the kits contain instructions is not considered to provide a patentable limitation (citing to *In re Ngai*, *supra*).

Menges allegedly teaches that the PAI promoter polymorphism 4G/5G is thought to play a role in prognosis of survival after severe trauma. Subjects with the 4G/4G genotype were more likely to have sepsis and multiorgan failure than subjects with the 5G/5G genotype (Table). Menges also allegedly teaches isolation of genomic DNA. **Menges admittedly does not teach** a kit using a proof reading polymerase (*i.e.*, as recited in claims 34 and 39).

However, **Xu** allegedly disclose a method and kit useful for detection and identifying variants of a nucleic acid (citing to page 2). Xu allegedly teaches that its method overcomes the shortcomings of **Menges** including cost, long analysis time, need for radiolabeled reagents, complexity and/or being poorly suited for multiplex analysis.

GenBank Sequence teaches instant SEQ ID NO:1, including the 4G/5G site.

From the foregoing, the Office has concluded that it would have been *prima facie* obvious to include oligonucleotides and proofreading polymerases in a kit as taught by Xu to analyze mutation in the PAI-1 gene in LD with position 12580 of SEQ ID NO:1. The artisan would have a reasonable expectation of success because he is merely using known methods to detect known mutations.

B. <u>Second Obviousness Rejection</u>

Claims 20-22, 25, 29-33, 35 are rejected as being obvious over **Henry** (*supra*) in view **GenBank Sequence** (Accession AF386492.2 GI:14488407 (*supra*) and Chee *et al.* (WO 95/11995) (hereinafter, "**Chee**")

The Action again references MPEP 2111.02 as above regarding preambles and concludes, as above that the language "a kit useful for determining a genotype of a subject … at nucleotide position 12580 of SEQ ID NO:1" merely sets forth the intended use or purpose of the claimed kit. Further, as above, claims 20-22, 25, 29-33 and 35 contain no structural requirements to distinguish them from a composition . Accordingly, the Office interprets the claims as encompassing a composition containing the claimed molecule.

With regard to claim 25 and 29, the presence in the kit of instructions is not considered by the Office to provide a patentable limitation (citing to *Ngai*, *supra*) as above

The Action refers to claim 41.

(which does not appear to be included in this rejection! Moreover, Applicants do not understand how the Office's discussion in the paragraph below relates to this claim.)

> The Action notes that claims directed to an apparatus must be distinguished from the prior art in terms of structure rather than function." *In re Schreiber,* 128 F.3d 1473, 1477-78,44

USPQ2d 1429, 1431-32 (Fed. Cir. 1997). In addition, "[A]pparatus claims cover what a device *is,* not what a device *does." Hewlett-Packard* Co. *v. Bausch &Lomb Inc.,* 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990) (emphasis in original). The Office contends that a prior teaching of the structural elements of the kit would render the instant claims obvious.

Allegedly, **Henry** teaches that (a) PAI-1 has been implicated in insulin resistance, coronary heart disease and inflammatory status (pg. 84, 1st column), (b) there is accumulating evidence that genetic control plays a role in circulating PAI-1 levels and (c) eight polymorphisms have been identified (pg 84, 2nd column). **Henry admittedly does not teach**

(1) detecting a polymorphic site at positions 12219 or 12580

(2) an oligonucleotide selected from SEQ ID NO:2-SEQ ID NO:11, or

(3) sequencing.

Chee is cited for the following disclosure:

(a) an array of capture probes (Fig. 16,and page 79 lines 23-39) and block tiling arrays (Fig. 7 and page 37 line 10- page 38 line 34); The block-tiling array allows the interrogation of multiple nucleotide sites by multiple probe sets, which represent every permutation of nucleotides possible for a give sequence. The tiling arrays o result in sequencing by hybridization of the entire sequence of interest.

(b) use of immobilized arrays to interrogate a reference sequence and its codons with a target sequence for the identification of single base mutants possible in the reference sequence which can be associated with disease (pg 31, lines 6-7; pg. 11 line 9-10);

(c) this approach allows simultaneous detection and quantification of multiple target sequences (pg 32 lines18-19), which would allow for sequence determination.

(d) a method of mutation detection for analyzing known target sequences for individual mutant sites and immediately adjacent bases (pg 18, lines 1-8).

(e) determination of all possible combinations of nucleotides surrounding a SNP, allowing determination of all possible nucleic acids.

(f) use of capture probes of 15 to 30 nucleotides, perfectly complementary to the interrogated DNA (see page 27 lines 2-6).

The Office concluded from the foregoing that it would have been *prima facie* obvious to examine the PAI-1 sequence (known from **GenBank sequence)** by the method of **Chee**. Motivation allegedly comes from the motivation to determine/identify additional mutations in the PAI-1 that could account for the alterations in PAI-1 activity associated alter PAI-1 levels in conditions including diabetes, inflammation and sepsis as taught by **Henry**. The tiling array of **Chee** applied to

the known PAI-1 sequence would result in a kit containing a microarray with probes that would allow for detection of any polymorphism in the sequence by using a tiling sequencing array, thus rendering the instant claims obvious.

Applicants' Response to both Obviousness Rejections

Amended claims 20 and 36 now recite all of the polymorphisms which have been identified for the first time by the present inventors as being relevant to a subject's ability to recover from an inflammatory condition. This is not taught or suggested in the prior art and the significance of these polymorphisms was not appreciated prior to the disclosure of the present invention.

The sequence of the human PAI gene was known, but there was no reason or basis to test for the presence of the presently claimed in a kit for detecting these SNPs (at position 12580 *et al.*) Thee would have been no reason to make oligos specific for identifying these SNPs before the present invention because there was no reason to determine the presence of these SNPs (and their alternative alleles) prior to the present application. The PAI-1 polymorphism that had medical interest, *i.e.*, utility, prior to this application was the "4G/5G" of the cited art (at position 837 of SEQ ID NO:1). Since no other SNPs, such as those recited in the present claims, were known to be associated with a clinical condition, there was no reason to look at the claimed SNPs and no reason to compile a kit for this purpose.

The Office has provided no rationale or basis for testing other polymorphisms in PAI-1 besides 4G/5G **(Henry, Menges)** in association with inflammatory disease, *a fortiori* the specific polymorphisms claimed in the amended claims as predictive of severity of or recovery from inflammatory disease. Therefore, the combination based on **Henry** and on **Menges** fail to provide an adequate basis for a *prima facie* obviousness rejection.

Chee does not teach any PAI-1 sequences, but only a general method for nucleic acid sequence analysis using DNA chips, which, in theory could be used to analyze the PAI-1 genes. Oligos used in this method of detection could be made by any number of known methods. However, prior to the patient information provided by the present application, there was no reason (or known utility) for analyzing the claimed SNPs for predicting patient outcomes with respect to inflammatory disorders. No one would have had any reason to do so, given only the knowledge that:

(1) PAI-1 is associated with fibrinolysis; and

(2) **Henry**, **Menges** and others disclosed association between a **distinct** PAI-1 polymorphism (4G/5G), PAI-1 protein levels and deep venous thrombosis; stroke; acute myocardial

infarction; late lumen loss after coronary artery stent placement; sudden cardiac death; survival in severe trauma patients; survival in meningococcemia patients; and PAI-1 levels in patients with acute lung injury.

However, there would be no reason to suspect, nor basis to conclude, that the claimed polymorphisms would be useful but for the first disclosure of the patient outcomes in the present application.

Applicants note that the language "genotype is prognostic of the subject's ability to recover from an inflammatory condition" in claim 20 has been moved from the preamble and placed in the body of the claim (in a "wherein clause"). Therefore, in contrast to the situation where language is in a claim preamble, this language must be construed as a proper limitation of the claim.

Brief Discussion of *In re Ngai*

In *Ngai*, the instructions were not considered to be "functionally related" to the kit (as they were merely the printed steps of the method claims). However, in Ngai, the analysis was under §102, not § 103, where the product was known. The Federal Circuit took the position that Ngai *et al.* were not "entitled to patent a known product by simply attaching a set of instructions to that [known] product."

In contrast,, the present claims recite restriction enzymes or oligos that are **specific** for the several particular polymorphisms recited in the claims. Those polymorphisms on their own are not a "product" as in *Ngai* where the elements of the claimed kit were known in the form of a kit, but for a different use. The present claims do not relate to any known use for the oligonucleotides (or restriction enzymes) -- as the oligos themselves would be novel (and unobvious) because, prior to the present invention, no one would have considered interrogating these particular polymorphisms and using the knowledge to predict recovery from inflammatory disease.

In further contrast to *Ngai*, the instruction element of the present kits (amended claim 25 *et seq.)* relate to their applicability for interpreting results obtained by using the kits to detect the relevant polymorphisms. This makes them "functionally related" to the kit, a relationship said to be lacking in the *Ngai* instructions.

For the reasons provided above, the rejection under §103 may properly be withdrawn.

VI. CONCLUSION

Applicants respectfully entry of the present amendments and remarks. In view of theses amendments, as discussed above, the claims are now free of the latest objections and rejections, and should therefore be allowed. Such reconsideration and allowance is respectfully requested.

The Examiner is respectfully requested to contact the undersigned at the phone number shown below if it would be helpful in advancing this case to allowance.

Respectfully submitted,

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